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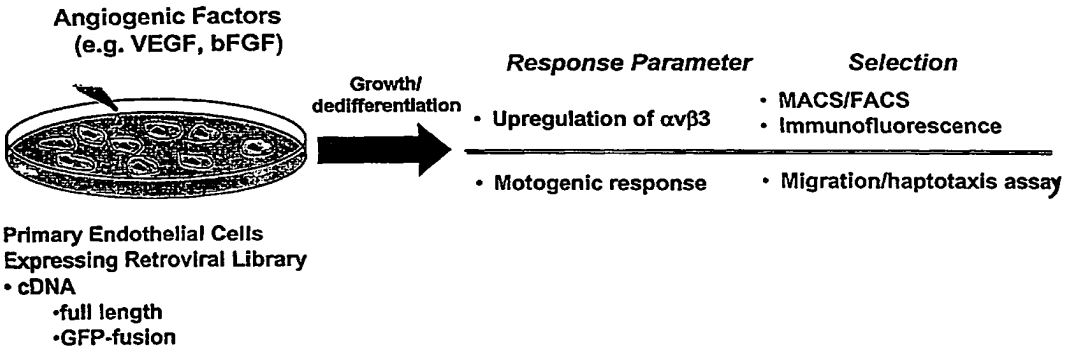
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),

[Continued on next page]

(54) Title: MODULATORS OF ANGIOGENESIS



(57) Abstract: The present invention relates to regulation of angiogenesis. More particularly, the present invention is directed to nucleic acids encoding "angiogenesis regulatory proteins and nucleic acids" which are involved in modulation of angiogenesis. The invention further relates to methods for identifying and using agents, including small organic molecules, antibodies, peptides, cyclic peptides, nucleic acids, antisense nucleic acids, RNAi, and ribozymes, that modulate angiogenesis via modulation of angiogenesis regulatory proteins and nucleic acids; as well as to the use of expression profiles and compositions in diagnosis and therapy of diseases related to angiogenesis.

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European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
18 November 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/27523

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C12P 21/06; C12N 15/00, 5/00, 15/63; C07H 21/02, 21/04
US CL : 435/69.1, 320.2, 325, 455, 375; 536/23.1, 23.5
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/69.1, 320.2, 325, 455, 375; 536/23.1, 23.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ALESSI P. et al. Molecular targeting of angiogenesis Biochimica et Biophysica Acta. March 2004, Vol 1654, pages 39-49, see entire document.	1-3, 5-6, 16, 18 and 20-32
A	Database GenEMbl on GenCore. AN: BC025358, November 2003, STRAUSBERG RL et al. Homo sapiens ATP-binding cassette, sub-family D (ALD), member1, mRNA(cDNA clone MGC:39449 IMAGE:4907640), complete cds. see nucleotide sequence which matches SEQ ID NO:3 of instant application.	1-3, 5-6, 16, 18 and 20-32

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
22 July 2004 (22.07.2004)

Date of mailing of the international search report
08 OCT 2004

Name and mailing address of the ISA/US
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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/06218

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 13,14,16-24,32-40,42-57 and 63-68
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/[redacted]7523

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Claim(s) 1-3, 5-6, 16, 18, 20-32 drawn to a method of identifying a compound that modulate angiogenesis, the method comprises contacting the compound with a nucleic acid sequence that hybridizes to the nucleic acid sequence selected from Group : -

1. SEQ ID NO:3,
2. SEQ ID NO:32,
3. SEQ ID NO:43,
4. SEQ ID NO:57,
5. SEQ ID NO:63,
6. SEQ ID NO:68,
7. SEQ ID NO:70,
8. SEQ ID NO:76,
9. SEQ ID NO:81,
10. SEQ ID NO:86,
11. SEQ ID NO:89,
12. SEQ ID NO:120,
13. SEQ ID NO:128,
14. SEQ ID NO:139,
15. SEQ ID NO:153,
16. SEQ ID NO:163,
17. SEQ ID NO:165,
18. SEQ ID NO:169,
19. SEQ ID NO:171,
20. SEQ ID NO:173,
21. SEQ ID NO:175,
22. SEQ ID NO:183,
23. SEQ ID NO:202,
24. SEQ ID NO:210,
25. SEQ ID NO:218,
26. SEQ ID NO:227,
27. SEQ ID NO:232,
28. SEQ ID NO:248,
29. SEQ ID NO:274,
30. SEQ ID NO:285,
31. SEQ ID NO:286,
32. SEQ ID NO:297,
33. SEQ ID NO:307,
34. SEQ ID NO:308,
35. SEQ ID NO:317,
36. SEQ ID NO:318,
37. SEQ ID NO:320,
38. SEQ ID NO:323,
39. SEQ ID NO:324,
40. SEQ ID NO:329,
41. SEQ ID NO:330,
42. SEQ ID NO:340,
43. SEQ ID NO:351,
44. SEQ ID NO:365,
45. SEQ ID NO:377,

46. SEQ ID NO:384,
47. SEQ ID NO:406,
48. SEQ ID NO:408,
49. SEQ ID NO:419,
50. SEQ ID NO:421,
51. SEQ ID NO:428,
52. SEQ ID NO:437,
53. SEQ ID NO:439
54. SEQ ID NO:445,
55. SEQ ID NO:456,
56. SEQ ID NO:462,
57. SEQ ID NO:481,
58. SEQ ID NO:484,
59. SEQ ID NO:493,
60. SEQ ID NO:496,
61. SEQ ID NO:498,
62. SEQ ID NO:519

Claims 1-17, 19-24 25-32 drawn to a method of identifying a compound that modulate angiogenesis, the method comprises contacting the compound with a polypeptide encoded by a nuclei acid sequence that hybridizes to the nucleic acid sequence selected from Group : -

63. SEQ ID NO:4,
64. SEQ ID NO:33,
65. SEQ ID NO:44,
66. SEQ ID NO:58,
67. SEQ ID NO:64,
68. SEQ ID NO:69,
69. SEQ ID NO:71,
70. SEQ ID NO:77,
71. SEQ ID NO:82,
72. SEQ ID NO:87,
73. SEQ ID NO:90,
74. SEQ ID NO:121,
75. SEQ ID NO:129,
76. SEQ ID NO:140,
77. SEQ ID NO:154,
78. SEQ ID NO:164,
79. SEQ ID NO:170,
80. SEQ ID NO:172,
81. SEQ ID NO:174,
82. SEQ ID NO:176,
83. SEQ ID NO:184,
84. SEQ ID NO:203,
85. SEQ ID NO:287,
86. SEQ ID NO:298,
87. SEQ ID NO:309,
88. SEQ ID NO:319,
89. SEQ ID NO:325,
90. SEQ ID NO:331,
91. SEQ ID NO:341,
92. SEQ ID NO:352,
93. SEQ ID NO:366,
94. SEQ ID NO:378,
95. SEQ ID NO:385,
96. SEQ ID NO:407,
97. SEQ ID NO:409,
98. SEQ ID NO:420,
99. SEQ ID NO:429,
100. SEQ ID NO:438,
101. SEQ ID NO:440,
102. SEQ ID NO:446,
103. SEQ ID NO:457,

104. SEQ ID NO:463,
105. SEQ ID NO:482,
106. SEQ ID NO:485,
107. SEQ ID NO:494,
108. SEQ ID NO:497,
109. SEQ ID NO:499,
110. SEQ ID NO:520

Claims 33, drawn to a method of modulating angiogenesis in a subject by administering a therapeutic effective amount of a polypeptide encoded by a nucleic acid sequence which hybridizes to the nucleic acid sequence selected from Group : -

111. SEQ ID NO:63,
112. SEQ ID NO:76,
113. SEQ ID NO:81,
114. SEQ ID NO:86,
115. SEQ ID NO:89,
116. SEQ ID NO:120,
117. SEQ ID NO:128,
118. SEQ ID NO:165,
119. SEQ ID NO:183,
120. SEQ ID NO:202,
121. SEQ ID NO:218,
122. SEQ ID NO:232,
123. SEQ ID NO:274,
124. SEQ ID NO:285,
125. SEQ ID NO:286,
126. SEQ ID NO:297,
127. SEQ ID NO:317,
128. SEQ ID NO:318,
129. SEQ ID NO:320,
130. SEQ ID NO:323,
131. SEQ ID NO:324,
132. SEQ ID NO:340,
133. SEQ ID NO:377,
134. SEQ ID NO:384,
135. SEQ ID NO:406,
136. SEQ ID NO:408,
137. SEQ ID NO:439
138. SEQ ID NO:445,
139. SEQ ID NO:456,
140. SEQ ID NO:481,
141. SEQ ID NO:484,
142. SEQ ID NO:493,
143. SEQ ID NO:496,
144. SEQ ID NO:498.

Claims 34, drawn to a method of modulating angiogenesis in a subject by administering a therapeutic effective amount of a nucleic acid sequence which hybridizes to the nucleic acid sequence selected from Group : -

145. SEQ ID NO:3,
146. SEQ ID NO:32,
147. SEQ ID NO:43,
148. SEQ ID NO:57,
149. SEQ ID NO:63,
150. SEQ ID NO:68,
151. SEQ ID NO:70,
152. SEQ ID NO:76,
153. SEQ ID NO:81,
154. SEQ ID NO:86,
155. SEQ ID NO:89,
156. SEQ ID NO:120,
157. SEQ ID NO:128,
158. SEQ ID NO:139,
159. SEQ ID NO:153,

160. SEQ ID NO:163,
161. SEQ ID NO:165,
162. SEQ ID NO:169,
163. SEQ ID NO:171,
164. SEQ ID NO:173,
165. SEQ ID NO:175,
166. SEQ ID NO:183,
167. SEQ ID NO:202,
168. SEQ ID NO:210,
169. SEQ ID NO:218,
170. SEQ ID NO:227,
171. SEQ ID NO:232,
172. SEQ ID NO:248,
173. SEQ ID NO:274,
174. SEQ ID NO:285,
175. SEQ ID NO:286,
176. SEQ ID NO:297,
177. SEQ ID NO:307,
178. SEQ ID NO:308,
179. SEQ ID NO:317,
180. SEQ ID NO:318,
181. SEQ ID NO:320,
182. SEQ ID NO:323,
183. SEQ ID NO:324,
184. SEQ ID NO:329,
185. SEQ ID NO:330,
186. SEQ ID NO:340,
187. SEQ ID NO:351,
188. SEQ ID NO:365,
189. SEQ ID NO:377,
190. SEQ ID NO:384,
191. SEQ ID NO:406,
192. SEQ ID NO:408,
193. SEQ ID NO:419,
194. SEQ ID NO:421,
195. SEQ ID NO:428,
196. SEQ ID NO:437,
197. SEQ ID NO:439
198. SEQ ID NO:445,
199. SEQ ID NO:456,
200. SEQ ID NO:462,
201. SEQ ID NO:481,
202. SEQ ID NO:484,
203. SEQ ID NO:493,
204. SEQ ID NO:496,
205. SEQ ID NO:498,
206. SEQ ID NO:519

Claims 35-36, drawn to an isolated nucleic acid sequences or variants thereof selected from Group : -

207. SEQ ID NO:165,
208. SEQ ID NO:202,
209. SEQ ID NO:210,
210. SEQ ID NO:218,
211. SEQ ID NO:227,
212. SEQ ID NO:232,
213. SEQ ID NO:248,
214. SEQ ID NO:274,
215. SEQ ID NO:285,
216. SEQ ID NO:286,
217. SEQ ID NO:297,
218. SEQ ID NO:307,
219. SEQ ID NO:308,

220. SEQ ID NO:317,
221. SEQ ID NO:318,
222. SEQ ID NO:320,
223. SEQ ID NO:323,
224. SEQ ID NO:324,
225. SEQ ID NO:329,
226. SEQ ID NO:330.

Claims 37, drawn to an isolated polypeptide selected from Group : -
227. SEQ ID NO:287,
228. SEQ ID NO:298,
229. SEQ ID NO:309,
230. SEQ ID NO:319,
231. SEQ ID NO:325,
232. SEQ ID NO:331.

The inventions listed as Groups 1-232 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of Groups 1-62 are compounds that interacts with nucleic acid sequences.
The special technical feature of Groups 63-110 are compounds that interacts with polypeptides.
The special technical feature of Groups 64-144 is protein therapy.
The special technical feature of Groups 145-206 is gene therapy.
The special technical feature of Groups 207-226 are nucleic acid sequences.
The special technical feature of Groups 227-232 are polypeptide sequences.

This international searching authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2, and 13.3) for the reasons indicated below:

According to the guidelines in Section (9(i)(a) of Annex B of the PCT Administrative instruction, the special technical feature as defined by PCT Rule 13.2 shall be considered to be met when all the alternatives of a Markush-group are of similar nature. For chemical alternatives, such as the claimed sequences) the Markush group shall be regarded as being of similar nature when

(A) all alternatives have a common property or activity and

(B)(1) a common structure is present, i.e, a significant structure is shared by all of the alternatives or

(B)(2) in cases where the common structure cannot be the unifying criteria, all
alternatives belong to an art recognized class of compounds in the art to which the invention pertains.

The instant application claims multiple polynucleotide and polypeptide sequences, which are considered to lack unity because:

These sequences do not meet the criteria of (A), common property or activity or (B)(2) art recognized class of compounds. Each sequence behave in a different way in the context of the claimed invention. Each member of the class cannot be substituted, one for the other, with the expectation that the same intended result would be achieved.

Further, the sequences do not meet the criteria of (B)(1), as they do not share, one with another, a common core structure. Accordingly, unity of invention between the nucleotide and protein sequences is lacking and each sequence claimed is considered to constitute a special technical feature.

Continuation of B. FIELDS SEARCHED Item 3:
Databases: Medline, Caplus, STIC sequcnc database.
Search terms: Angiogenesis, ATP-binding cassette, screening, method, nucleic acid seqcncs of SEQ ID NO:3.